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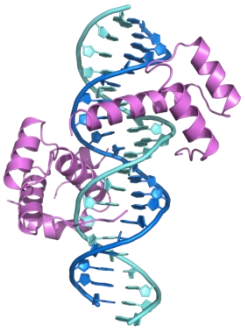
I seminari del DMMT,
Dipartimento di Medicina
Molecolare e Traslazionale



Brain-enriched orphan GPCRs: from signaling properties to control of mouse behavior

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19 Dicembre ore 12,30 - Aula B
Viale Europa 11

Tutti gli interessati sono invitati a partecipare

Ospite del Prof. Alessandro Barbon

Abstract

The molecular and cellular mechanisms that mediate the effects of stress in the brain leading to the development of affective disorders in a population of sensitive individuals are in large part uncharacterized. Some environmental factors have been linked to the etiology of major depressive disorder (MDD) as is the case of excessive administration of retinoic acid (RA), the active metabolite of vitamin A. This effect is partially explained by an RA-dependent inhibition of adult hippocampal neurogenesis, a process intimately involved with the development of depressive symptoms in human patients as well as in animal models of stress. However, the molecular players involved still need further characterization.

G Protein Coupled Receptors (GPCRs) regulate every aspect of neurophysiology and are the target of a third of FDA-approved drugs. However, the endogenous ligands activating ~100 GPCRs are still unknown, hence they are named orphan GPCRs. Nonetheless, the function of many orphan receptors has been linked to neurological disorders including MDD. Gprc5b, the most abundant orphan GPCR in the central nervous system, was originally identified as a retinoic acid-inducible GPCR, and its mRNA levels are altered in the brain of MDD patients, but pharmacological modulation of Gprc5b is limited by a lack of known endogenous/synthetic ligands. We found that chronic administration of RA in mice inhibited grooming behaviors in sucrose splash test and increased immobility time in tail suspension test while specifically up-regulating Gpr5cb levels in progenitor neurons within the subgranular zone of the hippocampal dentate gyrus. This area is considered a main hub of adult neurogenesis. Using knockout mouse models we are exploring how Gprc5b regulates adult neurogenesis in relation to behavioral responses affected by RA treatments and in naïve conditions measured with both traditional tests and innovative machine-learning-based approaches (DeepLabCut/Keypoint-Moseq). In parallel, we are exploring canonical and non-canonical signaling pathways modulated by Gprc5b using traditional and newly-developed cell-based assays. This work will possibly illuminate the biology of an understudied orphan GPCR with untapped pharmacological potential in the context of neuronal processes tightly associated with the etiology of MDD.